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EDITORIAL

Bronchial hyperresponsiveness, genetic predisposition and environmental factors: the importance of epidemiological research

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Bronchial hyperresponsiveness (BHR) is considered to be a major "marker" of airway dysfunction in asthma. BHR has also been postulated to be an important factor in the development of airways obstruction in chronic obstructive pulmonary disease (COPD); however, this has not yet been proved [1, 2]. Furthermore, BHR has been observed in subjects without a clinical diagnosis of asthma or COPD, and without respiratory symptoms, in general population studies. In addition, BHR is not always present in subjects reporting the diagnosis of asthma or asthma-like symptoms [2–5].

Thus, the role of BHR in the pathogenesis of asthma and COPD is not clear. In particular, we do not know whether BHR is an inborn characteristic, or if it could be acquired later in life as a consequence of the exposure to risk factors (infections, irritants, allergens, *etc.*). Both inborn and acquired conditions may have different degrees of importance, and they may interact or act independently to cause and/or modulate BHR. In recent years, epidemiological and basic research studies have been implemented with the aim of investigating the distribution of BHR in the general population in relation to different individual predisposing and environmental factors on the one hand and to inflammatory and/or immunological mechanisms on the other.

In this issue of the Journal, the paper by PEAT *et al.* [6] has provided an additional contribution to the epidemiological aspects related to BHR. It is important to note that they were able to perform histamine challenge tests in 4,366 children and 878 adults showing that bronchial reactivity by challenge test may be assessed in epidemiological studies. Additional studies have been performed in large samples from general population studies in recent years [2–5]. They have used different criteria for categorizing BHR in children and in adults. Indeed, there is not yet an agreement in the literature as to what BHR parameter is most sensitive and most specific [7]. At this stage, standardization of nonspecific challenge tests (nebulizers, dosimeters, long and short protocols, analysis of data, parameters to use, *etc.*) is necessary in epidemiological research to improve the comparability of the results from different studies.

The association between allergy and BHR has been confirmed [1, 6, 8–10]. Allergy in epidemiological studies is usually defined in terms of skin test positivity and/or increased level of total serum immunoglobulin E (IgE), parameters that also require a standardization procedure.

PEAT *et al.* [6] did not report results in relation to IgE. Therefore, there was no confirmation of the recent data of SEARS *et al.* [11] who found a significant association between increased serum IgE levels and increased BHR. Interestingly, SEARS *et al.* [11] also found this relationship in subjects without known presence of asthma or allergic diseases.

BURROWS *et al.* [12] pointed out that only increased levels of IgE are associated (from childhood to adulthood) with the diagnosis of asthma, whilst skin test positivity is associated with the diagnosis of rhinitis. In addition, the same authors demonstrated an increase of IgE in smokers, regardless of the presence of skin test positivity [13]. O'CONNOR *et al.* [14] reported increased BHR in smokers with atopy (as assessed by skin prick tests), but the level of IgE did not show an important contribution to BHR. A recent paper of TOLLERUD *et al.* [15] confirmed the association of serum IgE levels with the diagnosis of asthma. The importance of peripheral blood eosinophils was also pointed out by these authors, especially in relation to chronic phlegm production. Thus, it appears that the classical "markers" of allergy used in epidemiological studies may act independently and may not reflect the same expression of immunological alteration linked to BHR. Therefore, additional and new specific investigations and the determination of more sophisticated markers of allergy should be used in future epidemiological studies. In particular, the characterization of subsets of lymphocytes, radioallergosorbent test (RAST), mediators from eosinophils and mast cells, may help in understanding individual susceptibility and clarifying the relationship between allergy and BHR.

The importance of a familial predisposition and, therefore, a possible genetic transmission of BHR was also pointed out in the paper by PEAT *et al.* [6]. In fact, parental asthma was significantly associated with BHR. Indeed, other studies support the possibility of a genetic transmission of atopy and asthma [16]. The genetics of BHR appear complex. However, studies performed in twins and in members of same families suggest a possible genetic component in the regulation of BHR [17, 18].

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Familial concordance can also mean the sharing of a common environment and life style, which may contribute to the development of BHR or may modulate the degree of BHR. The paper by PEAT *et al.* [6], in part, addresses this important point. Data from occupational exposure clearly document that BHR may be acquired later in life, directly from exposure to specific air contaminants [19]. Air pollution is not considered in the paper by PEAT *et al.* [6], possibly because air pollutants (SO_2, NO_2, *etc.*) are not relevant in these towns in Australia. However, such exposures may be important in other cities, with raised levels of contaminants. Experimental data from animal models [20] and from controlled human exposure in volunteers [21], especially in susceptible subjects, support the hypothesis that some pollutants may affect bronchial responsiveness.

Epidemiological data suggesting a direct effect of air pollution on BHR are not reported. However, few studies report changes of peak expiratory flow variability when increased levels of pollution are present [22, 23]. Although, at present, chronic exposure to air pollution (*i.e.* living in highly polluted urban areas) has not been demonstrated to be associated with higher prevalence of BHR, epidemiological studies have shown higher prevalence of asthma and asthma symptoms in urban areas [24]. Exposure to passive smoking has been shown to be related to BHR in some studies [14, 25]; however, PEAT *et al.* [6] did not show any effects of environmental tobacco smoke on BHR. This negative result may be mainly ascribed to the information being obtained only in a subsample (1,217 children; 25% of the whole sample). In addition, factors which may interfere with the results, such as indoor environment, evaluation of correct reporting of smoking history, determination of markers of exposure (saliva or urine cotinine values) have not been considered.

On the other hand, PEAT *et al.* [6] observed the importance of respiratory infections during childhood, mainly <2 yrs of age, on the development of BHR. The role of respiratory infections in the determination of BHR has been recognized [26, 27]. Recently, MARTINEZ *et al.* [28] and YOUNG *et al.* [29] pointed out that respiratory infectious episodes during the first months of life are important in causing wheezy symptoms and BHR, respectively. In addition, MARTINEZ *et al.* [28] hypothesized that the anatomy of the airways may facilitate the development of infections. The official Report of the Surgeon General [30] clearly states that the exposure to environmental tobacco smoke is the cause of higher prevalences of respiratory infections in children. Hence, the results of PEAT *et al.* [6] may indirectly support the effect of passive smoking on BHR.

Conversely, the observation of a protective effect of a diet based on fish may again be ascribed to the limited data obtained in the same small subsample. Up to now, there are no data consistently supporting the hypothesis of a protection on the inflammatory mediators by a diet based on fish [31]; therefore, these results should be considered with caution and need to be confirmed.

Additional arguments must be considered when data on BHR are reported from epidemiological studies. The assessment of BHR by methacholine or histamine challenge tests, obtained only once and during a precise period of the year, may reflect a specific degree of BHR at that specific time. Since BHR shows marked temporal fluctuations in subjects with asthma, as recently reported by JOSEPHS *et al.* [32], a single evaluation of bronchial responsiveness should be considered only in the overall context of lung function and clinical assessment at that specific time.

In addition, fluctuations of BHR may be observed not only in patients with asthma, but also in other subjects depending on environmental conditions (exposure to irritants, infections, *etc.*). Again, the degree of exposure (duration of exposure and concentration of the irritant) may modulate the response of the airways, as well as the acute infectious episodes and their sequelae. In such conditions, the presence of late-phase reactions, based on inflammatory response, may be responsible for the increase of BHR.

An important additional factor to consider is the baseline level of lung function, which has been clearly documented to affect the response of nonspecific challenge test [1]. This observation must be considered in epidemiological studies, especially in non-asthmatic subjects (*e.g.* smokers), where anatomical alterations may be responsible for the reduction of airway calibre and, consequently, partially responsible for the increased responsiveness.

In conclusion, the paper by PEAT *et al.* [6], despite the limitations mentioned, points out the importance of continuing research through epidemiological studies to improve knowledge of the natural history of BHR. Longitudinal studies using nested case-control, based on repeated evaluation of BHR, may help in understanding the time fluctuations of BHR in relation to environmental factors, both in subjects with clinical diagnosis of asthma and in those where BHR was a laboratory finding, without clinically relevant symptoms or diagnosis of asthma. In addition, prospective studies may help to understand the role of BHR in non-atopic subjects and in the natural history of COPD.

Finally, advanced molecular and biochemical techniques *i.e.*, the application of so-called molecular and biochemical epidemiology, may be used to identify some specific immunological and/or inflammatory marker involved in the pathogenetic mechanisms, thus, facilitating early detection of subjects with individual susceptibility.

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